

ONC-A0310P

4/7

PCT REQUEST

Original (for SUBMISSION)

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application ONCOTHERAPY SCIENCE, INC. is entitled to claim priority of earlier application No. 60/538,658 by virtue of the following:
VIII-3-1(i v)		an assignment from NAKAMURA, Yusuke to ONCOTHERAPY SCIENCE, INC., dated 20 January 2004 (20.01.2004)
VIII-3-1(i v)		an assignment from FURUKAWA, Yoichi to ONCOTHERAPY SCIENCE, INC., dated 20 January 2004 (20.01.2004)
VIII-3-1(i v)		an assignment from NAKAMURA, Yusuke to JAPAN AS REPRESENTED BY THE PRESIDENT OF THE UNIVERSITY OF TOKYO, dated 19 January 2004 (19.01.2004)
VIII-3-1(i v)		an assignment from FURUKAWA, Yoichi to JAPAN AS REPRESENTED BY THE PRESIDENT OF THE UNIVERSITY OF TOKYO, dated 19 January 2004 (19.01.2004)
VIII-3-1(i x)	This declaration is made for the purposes of:	AP: (BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

ONC-A0310P

5/7

PCT REQUEST

Original (for SUBMISSION)

VIII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application THE UNIVERSITY OF TOKYO is entitled to claim priority of earlier application No. 60/538,658 by virtue of the following:
VIII-3-2(vii)		transfer of entitlement from JAPAN AS REPRESENTED BY THE PRESIDENT OF THE UNIVERSITY OF TOKYO to THE UNIVERSITY OF TOKYO by way of Transfer of entitlement under the National University Corporation Law(Law No.112 of July 16, 2003), dated 01 April 2004 (01.04.2004)
VIII-3-2(i x)	This declaration is made for the purposes of:	all designations

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference ONC-A0310P	FOR FURTHER ACTION	See item 4 below
International application No. PCT/JP2005/001172	International filing date (day/month/year) 21 January 2005 (21.01.2005)	Priority date (day/month/year) 23 January 2004 (23.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ONCOTHERAPY SCIENCE, INC.		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	<p>This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 80%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input checked="" type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input checked="" type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
<input checked="" type="checkbox"/>	Box No. I	Basis of the report																							
<input checked="" type="checkbox"/>	Box No. II	Priority																							
<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																							
<input type="checkbox"/>	Box No. IV	Lack of unity of invention																							
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																							
<input type="checkbox"/>	Box No. VI	Certain documents cited																							
<input checked="" type="checkbox"/>	Box No. VII	Certain defects in the international application																							
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

<p style="text-align: center;">The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 338 82 70</p>	<p>Date of issuance of this report 24 July 2006 (24.07.2006)</p> <p>Authorized officer <div style="text-align: right;">Masashi Honda</div></p> <p>e-mail: pt08@wipo.int</p>
--	--

PATENT COOPERATION TREATY

REC'D 27 JUL 2005

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT WIPO PCT

To:

see form PCT/ISA/220

4/8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/JP2005/001172

International filing date (day/month/year)
21.01.2005

Priority date (day/month/year)
23.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12Q1/48, G01N33/574

Applicant
ONCOTHERAPY SCIENCE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Jenkins, G

Telephone No. +31 70 340-2608



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17-20

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 17-20

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5,7,9-11,13-15
	No: Claims	1-4,6,8,12,16
Inventive step (IS)	Yes: Claims	
	No: Claims	1-16
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1 DOCUMENTS

D1: WO 02/090578 A (CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED; CHROMA THERAPEUTICS L) 14 November 2002 (2002-11-14)

D2: REA STEPHEN ET AL: "Regulation of chromatin structure by site-specific histone H3 methyltransferases" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 406, no. 6796, August 2000 (2000-08), pages 593-599, XP002154907 ISSN: 0028-0836

2 NOVELTY

3 The polypeptide alluded to in claims 1-14 is neither structurally limited (e.g. claim 1.a.ii clearly covers any polypeptide sequence), nor functionally limited (all proteins share certain biological activities such as nutritional value). In sum, the polypeptide of claims 1-14 could be anything. As a result, the subject-matter of claims 1-4,6,8,12 is not novel in the sense of Article 33(2) PCT. D1 discloses: a method of measuring methyl transferase activity of SET proteins such as SET1 and SET2 using H3 lys 4 as a substrate and S-adenosyl-L-methionine as a cofactor (p. 51,52). A corresponding method, and implicitly a kit, for screening for modulators of methyl transferase activity is also disclosed (claims 2,3), as well as the use of the modulators in the treatment of cancers such as colon cancer (p. 34). Therefore, the subject-matter of claims 1-4,6,8,12 is not new in the sense of Article 33(2) PCT.

4 Furthermore, D1 discloses a peptide containing NHSCDPN (figure 1, sequence 6, NHSC region) and S-adenosyl-L-methionine (p. 51). Therefore, the subject-matter of claim 16 is not new in the sense of Article 33(2) PCT.

5 INVENTIVE STEP

6 Although the discovery that ZNFN3A1 has methyl transferase activity would appear not to be obvious from the prior art (D1, p. 2, paragraph 3; D2, p. 595, column 2,

paragraph 1, last sentence), the broad definition of the polypeptide renders the subject-matter of claims 5,7,9-11,13-15 either obvious in light of D1, or unlikely to be a solution to any technical problem over the whole of the claimed scope (see Item VIII). Consequently, the subject-matter of said claims is not inventive (Article 33(3) PCT).

7 INDUSTRIAL APPLICABILITY

- 8 The subject-matter of claims 1-16 is considered industrially applicable in the field of medicine (Article 33(4) PCT).

Re Item VII

Certain defects in the international application

- 9 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description.

Re Item VIII

Certain observations on the international application

- 10 **The scope of the claims must be commensurate with the contribution to the prior art (PCT Guidelines 5.52).** In this case, the application shows that ZNFN3A1 (surprisingly) has methyl transferase activity. However, the subject-matter of claims 1-14 extends to methods and kits involving any polypeptide. The methods and kits of claims 1-12 can plainly only work if the biological activity is **methyl transferase activity**, and the methods and kits of claims 13,14 can only work if the biological activity is **affinity for HSP90A** - i.e. the biological activity cannot simply be **any** biological activity. Furthermore, based upon the disclosure of the application, the skilled person would only reasonably consider using sequence variants that are **closely** related to wild-type ZNFN3A1 to find polypeptides with the aforementioned functions, at least more closely related to ZNFN3A1 than to a protein derived from **a completely different gene** - not any sequence variant as implied by expressions such as in claim 1.a.ii (any number of mutations). As such, the subject-matter of claims 1-14 is unsupported (Article 6 PCT), and undisclosed (Article 5 PCT) within

the application as a whole.

- 11 The approximate term "about" (at least about 80% homology) used in claims 1,8,9,13-15 is contrary to the requirements of clarity of Article 6 PCT.
- 12 The claims contain many expressions that are linguistically unclear (Article 6 PCT). As just a few cases in point: "the condition capable of methylation of the substrate" (claim 1,5,8), "an at least methylation region" (claim 2,10).
- 13 The subject-matter of claim 12 is dependent on claim 7. However, it would appear that it should be dependent on claim 8 instead. This results in a lack of clarity according to Article 6 PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference ONC-A0310P	FOR FURTHER ACTION	See item 4 below
International application No. PCT/JP2005/001172	International filing date (<i>day/month/year</i>) 21 January 2005 (21.01.2005)	Priority date (<i>day/month/year</i>) 23 January 2004 (23.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ONCOTHERAPY SCIENCE, INC.		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 8 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input checked="" type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input checked="" type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
<input checked="" type="checkbox"/>	Box No. I	Basis of the report																							
<input checked="" type="checkbox"/>	Box No. II	Priority																							
<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																							
<input type="checkbox"/>	Box No. IV	Lack of unity of invention																							
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																							
<input type="checkbox"/>	Box No. VI	Certain documents cited																							
<input checked="" type="checkbox"/>	Box No. VII	Certain defects in the international application																							
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%;">Date of issuance of this report 24 July 2006 (24.07.2006)</td> <td style="width: 50%;">Authorized officer Masashi Honda</td> </tr> <tr> <td colspan="2">e-mail: pt08@wipo.int</td> </tr> </table>	Date of issuance of this report 24 July 2006 (24.07.2006)	Authorized officer Masashi Honda	e-mail: pt08@wipo.int	
Date of issuance of this report 24 July 2006 (24.07.2006)	Authorized officer Masashi Honda				
e-mail: pt08@wipo.int					

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 27 JUL 2005

PC | WIPO | PCT

To:

see form PCT/ISA/220

4/8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/JP2005/001172

International filing date (day/month/year)
21.01.2005

Priority date (day/month/year)
23.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12Q1/48, G01N33/574

Applicant
ONCOTHERAPY SCIENCE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Jenkins, G

Telephone No. +31 70 340-2608



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17-20

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 17-20

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5,7,9-11,13-15
	No: Claims	1-4,6,8,12,16
Inventive step (IS)	Yes: Claims	
	No: Claims	1-16
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1 DOCUMENTS

D1: WO 02/090578 A (CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED; CHROMA THERAPEUTICS L) 14 November 2002 (2002-11-14)
D2: REA STEPHEN ET AL: "Regulation of chromatin structure by site-specific histone H3 methyltransferases" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 406, no. 6796, August 2000 (2000-08), pages 593-599, XP002154907 ISSN: 0028-0836

2 NOVELTY

3 The polypeptide alluded to in claims 1-14 is neither structurally limited (e.g. claim 1.a.ii clearly covers any polypeptide sequence), nor functionally limited (all proteins share certain biological activities such as nutritional value). In sum, the polypeptide of claims 1-14 could be anything. As a result, the subject-matter of claims 1-4,6,8,12 is not novel in the sense of Article 33(2) PCT. D1 discloses: a method of measuring methyl transferase activity of SET proteins such as SET1 and SET2 using H3 lys 4 as a substrate and S-adenosyl-L-methionine as a cofactor (p. 51,52). A corresponding method, and implicitly a kit, for screening for modulators of methyl transferase activity is also disclosed (claims 2,3), as well as the use of the modulators in the treatment of cancers such as colon cancer (p. 34). Therefore, the subject-matter of claims 1-4,6,8,12 is not new in the sense of Article 33(2) PCT.

4 Furthermore, D1 discloses a peptide containing NHSCDPN (figure 1, sequence 6, NHSC region) and S-adenosyl-L-methionine (p. 51). Therefore, the subject-matter of claim 16 is not new in the sense of Article 33(2) PCT.

5 INVENTIVE STEP

6 Although the discovery that ZNFN3A1 has methyl transferase activity would appear not to be obvious from the prior art (D1, p. 2, paragraph 3; D2, p. 595, column 2,

paragraph 1, last sentence), the broad definition of the polypeptide renders the subject-matter of claims 5,7,9-11,13-15 either obvious in light of D1, or unlikely to be a solution to any technical problem over the whole of the claimed scope (see Item VIII). Consequently, the subject-matter of said claims is not inventive (Article 33(3) PCT).

7 INDUSTRIAL APPLICABILITY

- 8 The subject-matter of claims 1-16 is considered industrially applicable in the field of medicine (Article 33(4) PCT).

Re Item VII

Certain defects in the international application

- 9 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description.

Re Item VIII

Certain observations on the international application

- 10 **The scope of the claims must be commensurate with the contribution to the prior art (PCT Guidelines 5.52).** In this case, the application shows that ZNFN3A1 (surprisingly) has methyl transferase activity. However, the subject-matter of claims 1-14 extends to methods and kits involving any polypeptide. The methods and kits of claims 1-12 can plainly only work if the biological activity is **methyl transferase activity**, and the methods and kits of claims 13,14 can only work if the biological activity is **affinity for HSP90A** - i.e. the biological activity cannot simply be **any** biological activity. Furthermore, based upon the disclosure of the application, the skilled person would only reasonably consider using sequence variants that are **closely** related to wild-type ZNFN3A1 to find polypeptides with the aforementioned functions, at least more closely related to ZNFN3A1 than to a protein derived from **a completely different gene** - not any sequence variant as implied by expressions such as in claim 1.a.ii (any number of mutations). As such, the subject-matter of claims 1-14 is unsupported (Article 6 PCT), and undisclosed (Article 5 PCT) within

the application as a whole.

- 11 The approximate term "about" (at least about 80% homology) used in claims 1,8,9,13-15 is contrary to the requirements of clarity of Article 6 PCT.
- 12 The claims contain many expressions that are linguistically unclear (Article 6 PCT). As just a few cases in point: "the condition capable of methylation of the substrate" (claim 1,5,8), "an at least methylation region" (claim 2,10).
- 13 The subject-matter of claim 12 is dependent on claim 7. However, it would appear that it should be dependent on claim 8 instead. This results in a lack of clarity according to Article 6 PCT.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 27 JUL 2005

PC | WIPO | PCT

To:

see form PCT/ISA/220

4/8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/JP2005/001172

International filing date (day/month/year)
21.01.2005

Priority date (day/month/year)
23.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12Q1/48, G01N33/574

Applicant
ONCOTHERAPY SCIENCE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Jenkins, G

Telephone No. +31 70 340-2608



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 17-20

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 17-20
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/JP2005/001172

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5,7,9-11,13-15
	No: Claims	1-4,6,8,12,16
Inventive step (IS)	Yes: Claims	
	No: Claims	1-16
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1 DOCUMENTS

D1: WO 02/090578 A (CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED; CHROMA THERAPEUTICS L) 14 November 2002 (2002-11-14)
D2: REA STEPHEN ET AL: "Regulation of chromatin structure by site-specific histone H3 methyltransferases" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 406, no. 6796, August 2000 (2000-08), pages 593-599, XP002154907 ISSN: 0028-0836

2 NOVELTY

3 The polypeptide alluded to in claims 1-14 is neither structurally limited (e.g. claim 1.a.ii clearly covers any polypeptide sequence), nor functionally limited (all proteins share certain biological activities such as nutritional value). In sum, the polypeptide of claims 1-14 could be anything. As a result, the subject-matter of claims 1-4,6,8,12 is not novel in the sense of Article 33(2) PCT. D1 discloses: a method of measuring methyl transferase activity of SET proteins such as SET1 and SET2 using H3 lys 4 as a substrate and S-adenosyl-L-methionine as a cofactor (p. 51,52). A corresponding method, and implicitly a kit, for screening for modulators of methyl transferase activity is also disclosed (claims 2,3), as well as the use of the modulators in the treatment of cancers such as colon cancer (p. 34). Therefore, the subject-matter of claims 1-4,6,8,12 is not new in the sense of Article 33(2) PCT.

4 Furthermore, D1 discloses a peptide containing NHSCDPN (figure 1, sequence 6, NHSC region) and S-adenosyl-L-methionine (p. 51). Therefore, the subject-matter of claim 16 is not new in the sense of Article 33(2) PCT.

5 INVENTIVE STEP

6 Although the discovery that ZNFN3A1 has methyl transferase activity would appear not to be obvious from the prior art (D1, p. 2, paragraph 3; D2, p. 595, column 2,

paragraph 1, last sentence), the broad definition of the polypeptide renders the subject-matter of claims 5,7,9-11,13-15 either obvious in light of D1, or unlikely to be a solution to any technical problem over the whole of the claimed scope (see Item VIII). Consequently, the subject-matter of said claims is not inventive (Article 33(3) PCT).

7 INDUSTRIAL APPLICABILITY

- 8 The subject-matter of claims 1-16 is considered industrially applicable in the field of medicine (Article 33(4) PCT).

Re Item VII

Certain defects in the international application

- 9 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description.

Re Item VIII

Certain observations on the international application

- 10 **The scope of the claims must be commensurate with the contribution to the prior art (PCT Guidelines 5.52).** In this case, the application shows that ZNFN3A1 (surprisingly) has methyl transferase activity. However, the subject-matter of claims 1-14 extends to methods and kits involving any polypeptide. The methods and kits of claims 1-12 can plainly only work if the biological activity is **methyl transferase activity**, and the methods and kits of claims 13,14 can only work if the biological activity is **affinity for HSP90A** - i.e. the biological activity cannot simply be **any** biological activity. Furthermore, based upon the disclosure of the application, the skilled person would only reasonably consider using sequence variants that are **closely** related to wild-type ZNFN3A1 to find polypeptides with the aforementioned functions, at least more closely related to ZNFN3A1 than to a protein derived from **a completely different gene** - not any sequence variant as implied by expressions such as in claim 1.a.ii (any number of mutations). As such, the subject-matter of claims 1-14 is unsupported (Article 6 PCT), and undisclosed (Article 5 PCT) within

the application as a whole.

- 11 The approximate term "about" (at least about 80% homology) used in claims 1,8,9,13-15 is contrary to the requirements of clarity of Article 6 PCT.
- 12 The claims contain many expressions that are linguistically unclear (Article 6 PCT).
As just a few cases in point: "the condition capable of methylation of the substrate" (claim 1,5,8), "an at least methylation region" (claim 2,10).
- 13 The subject-matter of claim 12 is dependent on claim 7. However, it would appear that it should be dependent on claim 8 instead. This results in a lack of clarity according to Article 6 PCT.

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SHIMIZU, Hatsushi
Kantetsu Tsukuba Bldg. 6F
1-1-1, Oroshi-machi
Tsuchiura-shi, Ibaraki 3000847
JAPON

Date of mailing (day/month/year) 12 April 2005 (12.04.2005)	
Applicant's or agent's file reference ONC-A0310P	IMPORTANT NOTIFICATION
International application No. PCT/JP05/001172	International filing date (day/month/year) 21 January 2005 (21.01.2005)
International publication date (day/month/year)	Priority date (day/month/year) 23 January 2004 (23.01.2004)
Applicant ONCOTHERAPY SCIENCE, INC. et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
23 January 2004 (23.01.2004)	60/538,658	US	03 March 2005 (03.03.2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Abbou Farid Facsimile No. +41 22 338 70 10 Telephone No. +41 22 338 8169
---	--